REMARKS

The Final Office Action of November 9, 2010, has been received and reviewed. All claims currently under consideration stand rejected. This application is to be amended as previously set forth. All claim amendments are made without prejudice or disclaimer. Basis for the amendments, and for new claims 12-15, can be found throughout the application, for example, in the original claims, and in the Specification, *e.g.*, at **[0010]**; **[0011]**; **[0018]**; **[0023]**; **[0029]-[0032]**; **[0039]-[0044]**; and **Table 1**. No new matter has been presented. Reconsideration is respectfully requested.

35 U.S.C. § 103(a)

Claims 1-11 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over U.S. Patent 3,556,739 to Baniel and Blumberg) (hereinafter "Baniel") in view of Raghavarao *et al.* (2003) Clean Tech. Env. Policy 5:136-41 (hereinafter "Raghavarao"), Persson *et al.* (1999) J. Chem. Tech. Biotechnol. 74:238-43 (hereinafter "Persson"), Ullmann *et al.* (1995) AlChE J. 41:488-500 (hereinafter "Ullmann), and U.S. Patent 4,233,210 to Koch (hereinafter "Koch") as evidenced by Stephenson (1993) J. Chem. Eng. Data 38:134-8 (hereinafter "Stephenson") and Davison *et al.* (1966) J. Chem. Eng. Data 11:404-6 (hereinafter "Davison"). Final Office Action, at page 3. Applicants respectfully traverse this rejection.

The Office acknowledges that Baniel does not disclose "extracting water from aqueous solutions of proteins," as is presently claimed. Id. However, the Office asserts that "it would have been obvious... to use an organic solvent such as glycol ether for aqueous protein extractions because thermoseparating phase separation methods are known in the art to be more cost-effective, fast and preserve the product during the extraction methods as suggested by Raghavarao, Persson, Koch and Ullmann. Further, glycol ethers are known in the art to be used in extraction phase methods as suggested by Baniel and Koch. Given the teachings and inherent properties disclosed by Stephenson and Davison, one of ordinary skill in the art would be capable of determining the temperature to perform such extraction processes as disclosed by Baniel, Raghavarao, Persson and Koch with a reasonable expectation of success in separating a

concentrated aqueous protein phase from a liquid organic phase." Id., at page 7. In response to the applicants' previous remarks, the Office notes that reasoning taking into account only knowledge in the art prior to the applicants' disclosure is not impermissible. Id., at pages 7 and 8. The Office asserts that the applicants' previous remarks were directed "against the references individually," and further asserts that "no specific glycol ether [is] claimed and thus glycol ether is given its broadest interpretation." Id., at page 9.

To establish a *prima facie* case of obviousness, the prior art itself or "the inferences and creative steps that a person of ordinary skill in the art would [have] employ[ed]" at the time of the invention are to have taught or suggested the claim elements. Inherent properties of a claimed invention that are disclosed in the application, even if not explicitly recited in a claim, must be considered part of the claimed invention "as a whole." MPEP § 2141.02(I). Obviousness cannot be predicated on what is not known at the time an invention was made, even if the inherency of a certain feature is later established. MPEP § 2141.02(V).

The mere fact that references can be combined or modified does not render the resulting combination obvious unless the results would have been predictable to one of ordinary skill in the art. MPEP § 2143.01(III); KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385, 1396 (2007). Modifications of prior art references may only support a *prima facie* obviousness determination if there is a reasonable expectation of success in making the proposed modification. MPEP § 2143.02(I). There is no reasonable expectation of success in making a proposed modification to a reference when the resulting modification would be inoperable. Nor can a proposed modification to a reference change its principle of operation to support a rejection under 35 U.S.C. § 103. MPEP § 2143.01(VI).

Furthermore, in order to avoid the use of statutorily prohibited hindsight, the Office is instructed to determine the content of *the prior art as a whole* at the time an invention was made, including teachings of the prior art that would lead one of ordinary skill in the art away from the claimed combination. MPEP §§ 2141(II)(B); 2141.01(III); and 2141.02. For example, a claim is not obvious in view of a reference that teaches away from the claim. MPEP §§ 2144.02(VI) and 2145(X)(D)(2). A reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Baird, 16 F.3d 380 (Fed. Cir. 1994). A reference is said to

"teach away" when a person of ordinary skill, upon reading it, would be discouraged from following the path set out in the reference, "or would be led in a direction divergent from the path taken by the inventor." In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994); Monarch Knitting Mach. Corp. v. Sulzer Morat Gmbh, 139 F.3d 877 (Fed. Cir. 1998); Para-Ordnance Mfg. v. SGS Importers Int'l Inc., 73 F.3d 1085 (Fed. Cir. 1995).

Applicants respectfully submit that the present claims are non-obvious, notwithstanding the cited references, at least for the reason that the combination of the cited references, when considered in view of "the inferences and creative steps" that a person of ordinary skill would have employed at the time of the invention, do not teach or suggest the elements or inherent properties of the present claims. Furthermore, the Office has not presented a proper *prima facie* case of obviousness with regard to the present claims for at least the additional reason that the proposed combination impermissibly modifies the cited references.

The combination of cited references does not produce the claimed subject matter as a whole

As acknowledged by the Office, the present claims are drawn to methods "for extracting water from an aqueous solution of a protein," which do not necessarily accomplish protein purification or extraction. Final Office Action, at page 3. For example, the present claims involve removal of water from an aqueous protein solution- the claims do not recite that any proteins are separated from other proteins, or from impurity solutes. Furthermore, it is a further feature of the present claims (which is now explicitly recited in claim 1, as amended) that the protein in the separated concentrated aqueous protein phase is not significantly deactivated. As is explained in the Specification (*e.g.*, at **[0007]** and **[0010]**), this result represents a significant advance over the prior art that distinguishes the claimed invention from, for example, the cited references. In this regard, the applicants respectfully note that "[o]bviousness cannot be predicated on what is not known at the time an invention was made, even if the inherency of a certain feature is later established." MPEP § 2141.02(V). The applicants further note that, contrary to the Office's assertion at page 9 of the Final Office Action, specific glycol ethers are presently claimed; glycol ethers that have an inverse solubility in water, wherein the solubility of the glycol ether in water is at most 90% of the solubility of water in the glycol ether at the

temperature at which the intermixing is performed. None of the aforementioned claims elements and features is disclosed by the combination of cited references.

Applicants respectfully submit that, in order to demonstrate that the combination of references does not disclose the elements and features of the claims, it is necessary to consider what each reference discloses individually. For example, the framework used by the Office to make a determination of whether a claim is patentable under 35 U.S.C. § 103 includes "determining the scope and content of the prior art," and "ascertaining the differences between the claimed invention and the prior art." MPEP § 2141(II); Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966).

The Office characterizes Baniel as disclosing a method comprising the use of glycol ether as an organic solvent to "extract a product." Final Office Action, at page 5. The applicants respectfully submit that, at most, this characterization is misleading. First, the product that is extracted in Baniel is purified phosphoric acid, not a protein as is presently claimed. The applicants note that, regardless of how a small molecule acid is extracted from a solvent, such an extraction is not informative with regard to the extraction of water from an aqueous protein solution without deactivating the protein. This is the case for at least the reason that proteins in aqueous solution rely on proper folding and surface chemistry for their activity, which qualities are fragile during the procedures that were standard in the art prior to the present disclosure, and certainly long after 1972, when the Baniel Patent was issued. *See* Specifiation, *e.g.*, at **[0005]-[0007]**. The applicants respectfully submit that, if Baniel were able to be applied as broadly as suggested by the Office's combination with predictability and a reasonable expectation of success, the state of the art at the time the present application was filed would not have been so unsatisfactory.

Moreover, while Baniel lists glycol ethers among the organic solvent useful in its methods, the applicants note that glycol ether appear in a nearly limitless list that includes "esters, ketones and glycol ethers." Baniel, at Abstract; *see also* Baniel at col. 2, lines 37-46. In this regard, the applicants respectfully note that it cannot be obvious for one of skill in the art to select one alternative from a list provided in a reference when the skilled person must try each of numerous alternatives until arriving at a successful result, and the reference gives no indication

of which parameters were critical or which of many possible choices is likely to be successful. MPEP § 2145(X)(B). Furthermore, a reference that merely provides a "laundry list" of every possible alternative does not "reasonably lead" those skilled in the art to any particular alternative. Fujikawa v. Wattanasin, 93 F.3d 1559, 1571 (Fed. Cir. 1996).

In view of the foregoing, the applicants respectfully submit that Baniel, at most, discloses methods including mixing virtually any organic solvent with an aqueous solution comprising a small molecule, which methods are completely uninformative with regard to the extraction of water from an aqueous solution of biologically active protein without deactivating the protein, and which methods did not in fact lead to any advances in the art having any of the advantages of the presently claimed methods. Thus, for the combination of references cited by the Office to render any of the claims obvious, the deficiencies of Baniel must be remedied by the disclosure of one or more of the other cited references, or else be able to be deemed to have been, without any support in the record, within the inferences and creative steps that a person of ordinary skill in the art would have employed at the time of the invention

Neither does Raghavarao remedy the deficiencies of Baniel (and the rest of the Office's proposed combination). As the applicants have previously noted (*see* Applicants' Remarks of August 26, 2010, at page 8), the Office has incorrectly asserted that Raghavarao discloses "two phase extraction methods using glycol ethers." Final Office Action, at page 5. In fact, Raghavarao discloses two phase extraction methods using water-soluble polymers (*e.g.*, polyethylene glycols), not glycol ethers, and certainly not the glycol ethers that have the properties specifically recited in claim 1. Glycol ethers and polyethylene glycols have very different chemical properties that are relevant to the claimed methods. For example, glycol ethers are volatile organic solvents, and not polymers like polyethylene glycols. Raghavarao explicitly states that polyethylene glycols are used in their methods precisely for their difference from glycol ethers in this regard; the polymeric polyethylene glycols are provided in Raghavarao as alternatives to "volatile organic compounds as solvents." Raghavarao, at Abstract. Thus, Raghavarao certainly, when viewed as a whole, discourages the use of glycol ethers, and thereby teaches away from the present claims.

More fundamentally, the applicants further note that the aqueous two phase extraction of

Raghavarao (and also of Persson) merely selectively transfers proteins from one aqueous phase (rich in one type of water-soluble polymer or a salt) to another aqueous phase (rich in another type of water-soluble polymer or another salt). Water is present in both phases, but water does not transfer between the aqueous phases. Similarly, Ullmann discloses extraction of an organic solute from an aqueous solution into a solvent phase (*e.g.*, a solvent blend containing acetonitrile and methyl isobutyl ketone), without forming a stable emulsion or a concentrated aqueous protein phase, as is presently claimed. Moreover, Koch first precipitates protein before treating the precipitated protein with, for example, glycol ether in order to "isolate the accompanying substances in a fractionated way." Koch, at col. 2, lines 34-35. As acknowledged by the Office, Stephenson and Davison provide nothing towards the claimed subject matter than physical properties of certain glycol ethers. *See* Final Office Action, at page 7. Thus, none of the cited references, alone or in combination, discloses even the idea of extracting water from an aqueous protein solution (as is presently claimed), let alone the elements and features of the claimed methods.

Accordingly, the applicants respectfully submit that the difference between the all of the cited references in combination and the presently claimed subject matter is vast. Nowhere in the cited references is it even suggested to extract water from an aqueous protein solution. Unlike all of the cited references, the present claims involve the transfer of water out of an aqueous protein solution into a glycol ether solvent, without significant deactivation of the protein. In the claimed methods, all of the proteins in the original aqueous protein solution remain in the aqueous phase, so the purity of the protein fraction is unchanged. In other words, the applicants' claims are not drawn to an aqueous protein extraction method as stated by the Office, but an aqueous protein concentration method. The applicants demonstrated in the Examples that essentially none of the protein transfers into the glycol ether phase. Specification, at **Table 1**. This is in direct contrast to all of the cited references, because all of the cited references refer to the transfer of a solute (that is not a protein) out of a liquid phase into a solvent phase. These prior art examples do not involve transfer of water out of an aqueous feed solution to yield a more concentrated solution as recited in the claims of the present application. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 USC § 103(a) rejections

to the claims.

The proposed combination impermissibly modifies the cited references

As set forth, *supra*, Raghavarao discloses two phase extraction methods using water-soluble polymers (*e.g.*, polyethylene glycols) in a method that is incompatible with the presently claimed glycol ethers for the purposes of the Raghavarao reference. This is an additional reason why the Office has not presented a proper *prima facie* obviousness rejection.

Glycol ethers and polyethylene glycols have very different chemical properties that are relevant to the claimed methods. For example, glycol ethers are volatile organic solvents, and not polymers like polyethylene glycols. Raghavarao explicitly states that polyethylene glycols are used in their methods precisely for their difference from glycol ethers in this regard; the polymeric polyethylene glycols are provided in Raghavarao as alternatives to "volatile organic compounds as solvents." Raghavarao, at Abstract. In view of the importance of this difference between the glycol ethers of the present claims and the polymers used in Raghavarao, the applicants respectfully submit that it must be said that combining Raghavarao into a method using a glycol ether as a solvent would change the principle of operation in Raghavarao. Thus, Raghavarao cannot be used to support a rejection under 35 U.S.C. § 103 under the Office's examination guidelines. MPEP § 2143.01(VI).

For at least the foregoing reasons, the applicants respectfully submit that the Office has not presented a proper prima facie case that any of claims 1-11 are unpatentable under 35 U.S.C. § 103(a). Consequently, the applicants respectfully request the rejection of these claims under 35 U.S.C. § 103(a) be withdrawn.

Non-statutory double patenting rejection

Claims 1-11 stand provisionally rejected on the grounds of non-statutory obviousness-type double patenting over claims 1, 4-8, 10-14, and 16-20 of Application No. 10/590,185 (hereinafter "the '185 application"). Additionally, claims 1, 2, 5, 6, 8, 9, and 11 stand provisionally rejected on the grounds of non-statutory obviousness-type double patenting over

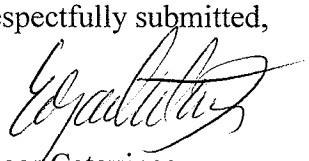
claims 1, 4, 6, 7, and 12 of Application No. 10/590,685 (hereinafter "the '685 application"). Applicants respectfully request that these non-statutory obviousness-type double patenting rejections be reconsidered in view of the present amendments. After reconsideration, should the Office determine that these non-statutory obviousness-type double patenting rejections are appropriate, the applicants respectfully request that these rejections be held in abeyance. Should this be the only remaining issue precluding patentability, the applicants reserve the right to file appropriate terminal disclaimers.

Rejoinder

Applicants respectfully submit that claim 1, which was identified by the Office as generic under the species election requirement of September 30, 2009, is in condition for allowance. Thus, the applicants respectfully request that claims 1-15, which depend from claim 1, be examined over their full scope.

If questions remain after consideration of the foregoing, the Office is kindly requested to contact the applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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